PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 28595P WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/09350	International filing date *(day/month/year)* 22.08.2003	Priority date *(day/month/year)* 23.08.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/68		
Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFT... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.03.2004	27.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Steinheimer-Breitkre Telephone No. +49 89 2399-7115

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09350

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-27 as originally filed

Claims, Numbers

1-15 received on 06.08.2004 with letter of 06.08.2004

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 15

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 1-14 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	1-5, 7-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	15
	No:	Claims	

2. Citations and explanations

see separate sheet

I Basis of the report

The amendments filed with the International Bureau under Article 19(1) introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 19(2) PCT. The amendments concerned are the following: Claims 1 and 15 have been amended whereby it is defined that the activatory processes are triggered by (1) non-apoptosis signals emanating from death receptors (which meets the requirements of Art. 19(2) PCT) and/or (2) non-apoptosis signals emanating from non-death receptor members of the TNF receptor family. Contrary to the applicants explanations, this **combination of non-apoptosis signals with said non-death receptors** (feature 2) is not disclosed in the context of the invention as described in the application as originally filed. In the following, the claims have been examined as if the latter amendment was not present.

III Non-establishment of opinion

Claims 1-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V Reasoned statement

V.1 Documents cited

Reference is made to the following documents:

D1: US-A-5 786 173 (ALNEMRI EMAD S ET AL) 28 July 1998 (1998-07-28)
D2: US-A-5 851 815 (ALNEMRI EMAD S ET AL) 22 December 1998 (1998-12-22)
D3: NARITA ET AL: 'Analysis of heat-shock related gene expression in head-and neck cancer using cDNA arrays' INT. J. RADIATION ONCOLOGY BIOL. PHYS, vol. 53, no. 1, 2002, pages 190-196, XP001135178
D4: US-B-6 171 8211 (KORNELUK ROBERT G ET AL) 9 January 2001 (2001-01-09)
D5: US-A-6 114 132 (FORD-HUTCHINSON ANTHONY ET AL) 5 September

2000 (2000-09-05)

D6: VILLA PASCAL ET AL: 'Caspases and caspase inhibitors.' TRENDS IN BIOCHEMICAL SCIENCES, vol. 22, no. 10, 1997, pages 388-393, XP002230757 ISSN: 0968-0004

V.2 Novelty, Inventive Step and Industrial Applicability (Art. 33 PCT)

2.1 The present application concerns the use of caspase-10 in monitoring and treatment of disease-associated activatory processes, wherein the activatory processes are triggered by non-apoptosis signals emanating from death receptors.

D1 and D2 disclose methods of monitoring and modulating disease-associated activatory processes comprising determining and/or influencing the amount or activity of Mch4 (which is the caspase-10a isoform) in a cell or an organism (D1: col. 8-12; D2: col. 7-11). Although it is not further specified in D1 and D2 that non-apoptosis signals are meant (and only apoptosis is discussed), the documents also address cancer and autoimmune diseases (D1: col. 8; D2: col. 2), which fall under the group of activatory processes that are also triggered by non-apoptosis signals, according to the present application. The present application is therefore not not clearly delimited from the methods of D1 and D2. Claims 1-5 and 7-14 therefore lack novelty in the light of D1 and D2.

Also **D3** discloses a method of monitoring and modulating disease-associated activatory processes comprising determining and/or influencing the amount or activity of caspase-10 in a cancer cell. Caspase-10 expression is modulated by heat-shock treatment and caspase-10 mRNA expression is measured (p. 193). D3 therefore appears to be novelty-destroying for claims 1-5, 7, 9, 10, 12 and 13.

For the sake of completeness, it is noted that also **D4** anticipates claims 1-5 and 7-14 (col. 3, 11 and 16).

2.2 D1, D2 and D5 describe methods of identifying and/or characterizing compounds for the modulation of disease-associated activatory processes comprising determining if a test compound is capable of influencing the activity of caspase-10 or caspase-10 isoform (D1: col. 16-17; D2: col. 9 and 15-16; D5: col. 6, 17 and 18).
Claim 15 of the present application further specifies that said activatory processes

are triggered by specific non-apoptosis signals. This feature is not explicitly present in the methods of D1, D2 or D5. However, the technical features of the claimed screening assay appear to be identical with the assays of the prior art. **Claim 15 therefore lacks novelty over D1, D2 and D5.**

It is noted that even if novelty was established for claim 15, the claim would lack an inventive step. D1 is considered to represent the closest prior art. Claim 15 of the present application is different from D1 in that it defines that said activatory processes are triggered by specific non-apoptosis signals. The effect should be that compounds are identified which influence specific non-apoptosis pathways.

It is however not specified in claim 15 how this effect is achieved i.e. the technical features of the claimed method are identical to conventional methods (see above), which identify both compounds which influence caspase 10 involving apoptosis signals or non-apoptosis signals (see also item 3.3). Thus, there is no technical effect (over the known methods) or the invention is not sufficiently dislcosed to allow for the assessment of a technical effect. Consequently, no inventive merit can be acknowledged.

It is acknowledged that the inventors have identified that caspase-10 plays a role in the mediation of cellular processes that are different from the induction of apoptosis. There is nevertheless no technical feature in the claims which could be taken to establish an inventive step in order to meet the requirements of the PCT.

2.3 The prior art as represented by D1-D6 is silent as to the following features:
The method of claim 5 wherein the disease is an inflammatory disease selected from skin inflammatory diseases and septic shock.
Claim 6 therefore appears to be novel.

2.4 Claim 6 concerns the method of claim 5 wherein the disease is an inflammatory disease selected from skin inflammatory diseases and septic shock. There is no information given in the application what surprising or unexpected effect is obtained when these diseases are selected. The selection appears to be arbitrary and lacks an inventive merit. Claim 6 is therefore not inventive.

2.5 For the assessment of the present claims **1-14** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to methods for diagnosing or treating a living subject. It is also noted that for medical use claims at the EPO, the compound that is used must be clearly defined. Furthermore, in second medical use claims, a therapeutic indication (disease to be treated) must be clearly specified rather than the physiological effect of the compound.

Claim 15 is considered to be industrially applicable.

V.3 The Applicant should also consider the following objections:

3.1 The term "caspase-10 or caspase-10 isoforms" in claims 1, 15 and 16 is not clear. From the description it seems that the 4 known caspase-10 isoforms (10a, 10b, 10c and 10d) are meant.
Furthermore, it appears from the description that also partial sequences (including short sequences of only 15 nucleotides) of caspase 10 are meant (p. 11). The description does however not contain any example on the use of such sequences. **The application therefore contravenes Art. 5 and 6 PCT.**

It is also noted that, if such sequences werer covered by the term caspase used in the claims, novelty and inventive step must be newly assessed.

3.2 The expression "disease-associated activatory process" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.

3.3 Claim 15 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved (finding compounds having certain properties), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

3.4 Contrary to the requirements of Rule 5.1 (a)(ii) PCT, the relevant background art disclosed in the documents D1-D6 is not mentioned in the description, nor are these document identified therein.

3.5 There is a mistake in the reference on p. 9, l. 29.

3.6 The application should only refer to published documents. The references ("supra") on p. 23, l. 25 and throughout the document should be completed or replaced by the corresponding published documents.

Claims

1. A method of monitoring and/or modulating disease-associated activatory processes comprising determining and/or influencing the amount and/or activity of caspase-10 or caspase-10 isoforms in a cell or an organism, wherein the activatory processes are triggered by non-apoptosis signals emanating from death receptors and/or non-apoptosis signals emanating from non-death receptor members of the TNF receptor family.

2. The method of claim 1 wherein the activatory processes are triggered by receptor-crosslinking.

3. The method of claim 1 or 2, wherein the activatory processes are triggered by non-apoptosis signals emanating from death receptors, particularly TRAIL-R1, TRAIL-R2, CD95, TNF-K1 (pSS TNF-R), TRAMD, DR6 or combinations thereof.

4. The method of claims 1 or 2, wherein the activatory processes are triggered by signals emanating from non-death receptor members of the TNF receptor family and/or members of the TLR receptor family.

5. The method of any one of claims 1 to 4, wherein the disease is selected from hyperproliferative, inflammatory and auto-immune diseases.

6. The method of claim 5, wherein the disease is an inflammatory disease selected from skin inflammatory diseases and septic shock.

7. The method of claim 5, wherein the disease is a hyperproliferative disease selected from tumors.

8. The method of claim 5, wherein the disease is an auto-immune disease.

9. The method of any one of claims 1 to 8 comprising monitoring the presence, amount, localization and/or activity of caspase-10 or caspase-10 isoforms in a sample.

10. The method of claim 9, wherein caspase-10 or caspase-10 isoforms are determined on the nucleic acid level.

11. The method of claim 9, wherein caspase-10 or caspase-10 isoforms are determined on the protein level.

12. The method of any one of claims 1 to 8 comprising modulating the amount and/or activity of caspase-10 or caspase-10 isoforms in a cell or an organism.

13. The method of claim 12, wherein the amount and/or activity of caspase-10 or caspase-10 isoforms is modulated on the nucleic acid level.

14. The method of claim 12, wherein the amount and/or activity of caspase-10 or caspase-10 isoforms is modulated on the protein level.

15. A method of identifying and/or characterizing compounds for the modulation of disease-associated activatory processes comprising determining if a test compound is capable of influencing the activity of caspase-10 or caspase-10 isoforms, wherein the activatory processes are triggered by non-apoptosis signals emanating from death receptors and/or non-apoptosis signals emanating from non-death receptor members of the TNF receptor family.